The Rejection of Claims 1, 2, 4, 5, 7-9, 11-14, 16, 23, 24, 26, 27, 29-31, 33-36 & 38 Under 35 U.S.C. § 103(a)

Claims 1, 2, 4, 5, 7-9, 11-14, 16, 23, 24, 26, 27, 29-31, 33-36 & 38 are rejected as obvious over Vary et al. in view of Lane et al. The rejection is respectfully traversed.

Claims 1 and 23 are the only independent claims of the rejected claim set. Claim 1 recites a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample. The method comprises the four steps of (i) amplifying a region of DNA comprising a polymorphic locus in the sample, (ii) labeling the amplified DNA products, (iii) hybridizing the labeled amplified DNA products to a probe on a solid support, and (iv) detecting the hybridized labeled amplified DNA products. The amplification is carried out using a pair of primers. The first primer terminates at its 3' end at the polymorphic locus and comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of the probe on the solid support and not complementary to the region of DNA. The step of amplifying produces a first strand and a second strand. The first strand comprises a portion identical to all or part of the probe, and the second strand comprises a 5' portion complementary to all or part of the probe. Claim 23 recites a method to prepare samples for analysis to determine a nucleotide at a polymorphic locus in a nucleic acid sample. The method comprises the three steps of amplifying, labeling, and hybridizing of claim 1, but does not require detecting.

Vary is cited as teaching "a method to determine a nucleotide at a polymorphic locus in a nucleic acid sample . . . the method comprising amplifying a region of DNA comprising the polymorphic locus . . . wherein the primer comprises a 3' portion which is complementary to the region of DNA . . . and a 5' portion which is complementary to all or part of a probe on a solid support and not complementary to the region of DNA . . ., labeling the amplified DNA to form

labeled amplified DNA products . . . and hybridizing the labeled DNA products to the probe on a solid support . . . ." Office action at page 3, citations to reference omitted. The Office Action admits that Vary does not teach a primer pair wherein the first primer comprises a 5' portion which is identical in sequence to all or portion of a probe on a solid support. That element of the rejected claims is allegedly provided by Lane. According to the Office Action at page 3, Lane teaches "a similar method to determine a nucleotide analyte comprising: amplifying a region of DNA comprising [sic] using a primer pair, wherein the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical to a portion of a probe on a solid support and not complementary to the region of DNA to form a first strand and a second strand wherein the first strand comprises a portion identical to all or part of the probe and the second strand comprises a 5' portion complementary to all or part of the probe; hybridizing the amplified products to the probe on the support such that the second strand hybridizes to the support; and detecting the amplified products wherein the presence of amplified products indicates the nucleic acid sample contains the nucleotide analyte (Column 8, lines 36-41 and 9B)."

In order to establish a *prima facie* case of obviousness, the PTO must make three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP 706.02(j). This rejection fails to make the first and third showings.

The combined teachings of Vary and Lane do not teach or suggest all limitations recited in the subject claims. The Office Action states that Lane teaches a primer having "a 5' portion

which is identical to a portion of a probe on a solid support and not complementary to the region of DNA". Office Action at page 3, lines 16-17, emphasis added. However, Lane actually teaches a primer with a portion which is identical to a portion of the probe and is complementary to a portion of the analyte (see Fig. 9B; Lane's "analyte" is the sample DNA). Lane's probe contains a single region which is both complementary to a region of the analyte and complementary to the primer. The subject claims, however, recite that "the first primer comprises a 3' portion which is complementary to the region of DNA and a 5' portion which is identical in sequence to all or part of a probe on a solid support and not complementary to the region of DNA". Emphasis added. In the subject claims, the 5' and 3' portions of the primer are distinct. One portion is complementary to a region of the DNA, and the other portion is not complementary to the region of DNA. These portions serve distinct functions. The 3' portion is complementary to the region of DNA to be amplified and serves the usual function of an amplification primer, *i.e.*, to specify the region to be amplified. However, the 5' portion serves as a tag which hybridizes to a probe at a known position on a solid support. The 5' tag portion of the primer is identical to all or part of a probe on a solid support; the identical portion is not complementary to the region of DNA, which distinguishes it clearly from the 3' portion that is complementary to the region of DNA. Lane teaches a primer portion which is simultaneously identical to a part of the probe and complementary to the region of sample DNA being amplified. The subject claims require two separate portions of the primer, and the claim specifically excludes the possibility that a single DNA sequence would serve both functions. Therefore, the combined teachings of Lane and Vary do not teach or suggest at least one limitation of the subject claims. For this reason alone, the *prima facie* case fails.

According to the Office Action, one of ordinary skill in the art would have been motivated to modify the method of Vary by using Lane's primer with a 5' portion that is identical to a probe on a solid support "to thereby immobilize the sense strand for the expected benefit [of] detecting the presence of a polymorphism in the coding strand." Office Action at page 3, last line, to page 4, line 1. The Office Action offers alternatively that the combination of the single primer amplification of Vary with the primer pair amplification of Lane would have the "obvious benefit of providing the second strand itself or in addition to the first strand to thereby more accurately determine the presence of the polymorphic locus by analyzing the presence and quantity of both the first and second strands." Office Action at page 4, lines 3-6.

It appears that the Office Action relies on impermissible hindsight to combine selected teachings of Lane with the method of Vary in order to arrive at the alternative advantageous uses described above. One of ordinary skill allegedly would find it obvious to use the identical primer portion of Lane in Vary's method either (i) in order to immobilize and detect the sense strand or (ii) to detect the second strand or both first and second strands. However, the Office Action provides no suggestion why one of ordinary skill would have selected Lane's primer portion which is identical to part of the probe in order to obtain either of the two advantages just mentioned. Lane appears to have been used merely to provide the missing puzzle piece that was needed to convert Vary's method into the method of the subject claims. Indeed, the differences between Vary's method and Lane's method make it difficult to combine them even if a proper motivation were supplied.

In Vary's method, only the amplified products hybridize to the probe. In contrast, Lane hybridizes the sample DNA to a probe on a solid support and then amplifies a region of the sample DNA at the location of the probe. According to Lane's method, the probe does not

interact at all with the amplification products. There is no suggestion in either Lane, Vary, or the prior art as a whole to include Lane's primer portion, which is identical to the probe, in the primer of Vary. The subject specification appears to have served as a template for insinuating Lane's primer into Vary's method in the rejection.

The remaining claims (2, 4, 5, 7-9, 11-14, 16, 24, 26, 27, 29-31, 33-36 & 38) of the rejected set are dependent from either claim 1 or claim 28 and recite additional elements. The Office Action states that either Vary or Lane provides teachings of those additional elements which, when combined with the teachings discussed above, render the dependent claims obvious. Without admitting to the appropriateness of those teachings in rejecting the dependent claims as discussed in the Office Action, Applicants respectfully submit that the arguments submitted above demonstrate that (1) the combined teachings fail to teach or suggest a primer having "a 5' portion which is identical to a portion of a probe on a solid support and not complementary to the region of DNA" as required by all of the dependent claims, and (2) there is no motivation to combine the teachings of Vary and Lane in the cited references or in the knowledge generally available.

Therefore, for the reasons discussed above, the withdrawal of this rejection is respectfully requested.

The Rejection of Claims 3, 10, 25 & 32 Under 35 U.S.C. § 103(a)

Claims 3, 10, 25 & 32 are rejected as obvious over Vary et al. in view of Lane et al., Hames et al., and Lapidus et al. This rejection is respectfully traversed.

Claims 3 and 25 recite the methods of claims 1 and 23, respectively, wherein the step of labeling is performed by a terminal transferase reaction. Claims 10 and 32 recite the methods of

claims 1 and 23 wherein the label is fluorescent and further recite the steps of optically detecting the fluorescent label on the solid support and determining the ratio of different allelic forms of the polymorphic locus from the relative amounts of label.

Regarding claims 3 and 25, the Office Action states that Vary and Lane do not teach the use of terminal transferase for labeling. Hames teaches the use of terminal transferase to label the 3' end of DNA molecules with a single radiolabeled nucleotide. However, as discussed above, the combined teachings of Vary and Lane would fail to teach or suggest a primer having "a 5' portion which is identical to a portion of a probe on a solid support and not complementary to the region of DNA" as required by the subject claims. Moreover, there is no proper motivation to combine the teachings of Vary and Lane because their methods are so distinct. Hames does not remedy these defects.

The Office Action states that the determination of fluorescent label at known locations on the solid support, as recited by claims 10 and 32, is taught by Lane. However, Lane does not appear to teach the comparison of fluorescent quantities to determine a ratio of nucleotides at a polymorphic locus. Lapidus teaches the comparison of amounts of fluorescent label to determine whether an individual is heterozygous or homozygous but does not remedy the defect in the rejection. This rejection, however, suffers from the same deficiency described above. The Office Action fails to assert a combination of references that teach all limitations of the claims. The combined teachings of Vary, Lane, and Lapidus fail to suggest a primer having "a 5' portion which is identical to a portion of a probe on a solid support and not complementary to the region of DNA".

Therefore, for the reasons discussed above, the withdrawal of this rejection is respectfully requested.

The Rejection of Claims 6 & 28 Under 35 U.S.C. § 103(a)

Claims 6 and 28 are rejected as obvious over Vary et al. in view of Lane et al. and Mullan. This rejection is respectfully traversed.

Claims 6 and 28 recite the methods of claims 1 and 23 wherein the nucleotide is enzymatically labeled. The Office Action states that Vary and Lane do not teach enzymatic labeling. Mullan teaches the use of enzyme-labeled oligonucleotide probes which bind to immobilized sample DNA but fails to remedy the defect in the primary references. The rejection fails because the references fail to teach or suggest a primer having "a 5' portion which is identical to a portion of a probe on a solid support and not complementary to the region of DNA".

Therefore, the withdrawal of this rejection is respectfully requested.

The Rejection of Claims 15 & 37 Under 35 U.S.C. § 103(a)

Claims 15 and 37 are rejected as obvious over Vary et al. in view of Lane et al. and Lockhart et al. This rejection is respectfully traversed.

Claims 15 and 37 recite the methods of claims 1 and 23 wherein the solid support is a microtiter dish. The Office Action states that Vary and Lane do not teach the use of a microtiter dish as the solid support. Lockhart teaches the use of plates which can have depressed regions. Lockhart, however, fails to remedy the defect in the primary references. Combination of Vary, Lane, and Lockhart fails to teach or suggest a primer having "a 5' portion which is identical to a portion of a probe on a solid support and not complementary to the region of DNA".

Therefore, the withdrawal of this rejection is respectfully requested.

Allowance of all pending claims is respectfully requested.

Respectfully submitted,

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By: _____
Lin J. Hymel
Registration No. 45,414

Banner & Witcoff, Ltd.
1001 G Street, N.W., Eleventh Floor
Washington, D.C. 20001-4597
(202) 508-9100